

PHOSPHODIESTERASE 5 INHIBITORS: CURRENT STATUS AND POTENTIAL APPLICATIONS

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Phosphodiesterase enzymes convert cyclic GMP and cyclic AMP to the corresponding nucleotide monophosphates. Phosphodiesterase 5 (PDE5) inhibition is now a widely accepted and efficacious therapeutic option for the treatment of erectile dysfunction in men, as a result of extensive clinical experience with sildenafil and other new PDE5 inhibitors. Research in the field continues at a substantial level to identify new, selective PDE5 inhibitors and to investigate their usefulness and activity in other areas. This review summarizes recent clinical trials with PDE5 inhibitors, advances in medicinal chemistry, and other activities and potential applications of this class of compounds.

CORPUS CAVERNOSUM
The vascular space in erectile tissue.

PENDANT
A functional group that is attached to another in a molecule.

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Phosphodiesterase enzymes convert the intracellular second messengers cyclic AMP and cyclic GMP to the corresponding nucleotides AMP and GMP. There are now 11 phosphodiesterase families, many of which exist as splice variants^{1,2} (TABLE 1). The cAMP-specific enzymes include phosphodiesterase 4 (PDE4), -7 and -8. The cGMP-specific PDEs are PDE5, -6 and -9, whereas PDE1, -2, -3, -10 and -11 use both cyclic nucleotides.

PDE5 was purified in 1980 by Francis and co-workers from rat lung³, and was first cloned by McAllister-Lucas *et al.* in 1993 (REF. 4). The enzyme is active as a homodimer, which has a molecular mass of approximately 200 kDa. Each monomer contains a carboxy-terminal catalytic domain, a highly conserved zinc-binding motif, two allosteric binding pockets for cGMP and — in the amino-terminal region — a phosphorylation site at serine 92 (Ser92). Either protein kinase A (PKA) or PKG can phosphorylate PDE5, and this results in a significant increase in PDE5 activity⁵. The protein is widely distributed throughout the smooth muscle in the body and is also found in platelets. Three different forms have been identified in the CORPUS CAVERNOSUM⁶ and two splice variants have also been identified^{7,8}.

Most known PDE5 inhibitors compete with the substrate cGMP for binding to the protein at the catalytic site. Although cGMP binding to the catalytic site

stimulates cyclic-nucleotide binding to the allosteric sites, inhibitors do not elicit the same property, and Ser92 phosphorylation has no effect on inhibitor binding⁵. Turko and co-workers used sildenafil (Viagra; compound 1 in FIG. 1) and zaprinast (compound 2) to propose a binding-site model for this class of compounds⁹. They propose that, for improved affinity, the PENDANT aromatic ring should incorporate hydrophobic substituents, and that a low net charge on the molecule is preferred. This report used PDE5 from bovine lung, and it was shown that similar K_i (enzyme inhibition constant) values were obtained with the same compounds using PDE5 from human corpus cavernosum.

An important issue in the development of PDE5 inhibitors is specificity for the other PDEs. The selectivity of the compounds discussed in this review has been measured against PDE1–4, and in some cases, PDE6. No data have been published for selectivity against PDE8–11. It has been reported that PDE11 closely resembles PDE5 (71% amino-acid similarity), and that the non-selective PDE inhibitor dipyrindamole inhibits PDE11A with an IC_{50} value (half-maximal inhibitory concentration) of 0.9 μ M (REF. 2). In spite of the similarity, there are important differences in the amino-acid sequence in the active site that allow PDE11A to hydrolyse both cAMP and cGMP.

Table 1 | **Phosphodiesterase enzymes**

PDE gene products	Substrate specificity	Consequence of inhibition
1A–C	cGMP, cAMP	Hypotension
2A	cAMP > cGMP	Unknown
3A–B	cAMP > cGMP	Inotrope, arrhythmia
4A–D	cAMP	Emesis, anti-inflammatory
5A	cGMP	Vascular relaxation
6A–C	cGMP	Visual disturbance, retinitis pigmentosa
7A	cAMP	Inhibition of T-cell activation
8A–B	cAMP	Unknown
9A	cGMP	Unknown
10A	cAMP > cGMP	Unknown
11A	cGMP, cAMP	Unknown

Adapted from REF. 56. cAMP, cyclic AMP; cGMP, cyclic GMP; PDE, phosphodiesterase.

As physiological roles for these phosphodiesterases are established, inhibitor discovery and specificity will have to be expanded to accommodate them. Although sildenafil has an acceptable degree of selectivity, increased specificity for PDE5, particularly over PDE1 and PDE6, is often a primary objective in the optimization of new inhibitors. Improved specificity over PDE6 will reduce or eliminate the incidence of visual disturbances associated with sildenafil. As the primary phosphodiesterase found in the plasma, PDE1 inhibition might be associated with the flushing and headaches that are observed with sildenafil. In the case of all the new PDE5 inhibitors that have been described in the peer-reviewed literature, improvements in selectivity were determined empirically, and compounds were optimized on the basis of structure–activity explorations of the chemical series in question. There has been some work devoted to understanding the basis of the substrate selectivity of the phosphodiesterase enzymes¹⁰. HYDROPATHY analysis of the catalytic domain of several phosphodiesterases indicated that the arrangement and nature of

HYDROPATHY

The analysis of the hydrophobic and hydrophilic characteristics of molecules.

HAEMODYNAMIC

Relating to physical aspects of blood circulation.

PRIAPRISM

A persistent erection of the penis resulting from causes other than sexual stimulation.

residues near glutamate 775 is a crucial determinant. In the case of cGMP-specific enzymes, a higher proportion of hydrophobic amino acids are found. This results in enhanced affinity for cGMP and also discriminates against cAMP binding.

PDE5 is the primary cGMP-hydrolysing activity in human corpus-cavernosum tissue. Erection is largely a HAEMODYNAMIC event, which is regulated by vascular tone and blood-flow balance in the penis. Because cGMP levels modulate vascular tone, it is an obvious target for therapeutic intervention in the process (FIG. 2). When a man is sexually stimulated, either physically or psychologically, nitric oxide (NO) is released from non-cholinergic, non-adrenergic neurons in the penis, as well as from endothelial cells. NO diffuses into cells, where it activates **soluble guanylyl cyclase**, the enzyme that converts GTP to cGMP. The cyclic nucleotide then stimulates PKG, which initiates a protein phosphorylation cascade. This results in a decrease in intracellular levels of calcium ions, leading ultimately to dilation of the arteries that bring blood to the penis and compression of the spongy corpus-cavernosum tissue. This compression contracts veins, which reduces the outflow of blood and increases intracavernosal pressure, resulting in an erection¹¹. A PDE5 inhibitor will retard enzymatic hydrolysis of cGMP in the human corpus cavernosum, leading to the same outcome.

It is essential to point out that a PDE5 inhibitor will function best when nerves innervating the penis are intact, and when circulatory function in the tissue is sufficient. Furthermore, a PDE5 inhibitor works in conjunction with sexual stimulation, unlike agents such as prostaglandin E2, which directly influence vascular tone. This results in a substantially lowered risk of PRIAPRISM. As discussed later in the manuscript, in spite of the presence of PDE5 in the general circulation, the use of PDE5 inhibitors in patients with cardiovascular disorders is generally considered safe, because these agents do not significantly affect blood pressure or heart rate if used alone. However, concurrent use with organic nitrates is contraindicated because of a synergistic effect on blood pressure.

This review provides an update on clinical studies with PDE5 inhibitors, including vardenafil (Nuviva; compound 3 in FIG. 1) and tadalafil (IC351, Cialis; compound 4 in FIG. 1), two compounds that are undergoing FDA review for approval for the treatment of erectile dysfunction (ED). In addition, advances in medicinal chemistry that have been published since 2001 (REF. 12) are discussed. The activity and potential usefulness of PDE5 inhibitors in other therapeutic areas is also summarized.

Clinical results

Sildenafil was approved for use in the United States in March 1998, and now accounts for more than 90% of all pharmaceutical sales for the treatment of ED. Worldwide sales in 2001 exceeded US \$1.5 billion. Because of its mechanism of action, sildenafil is contraindicated in patients taking NO donors or organic nitrates. The patient population with the greatest risk of developing

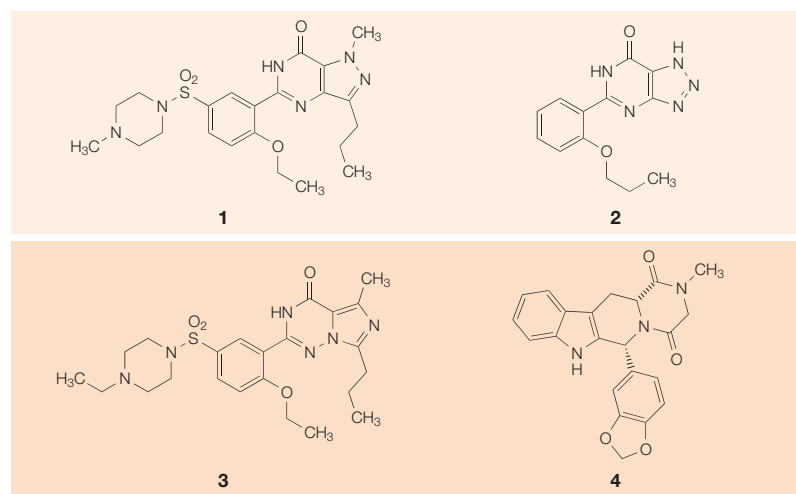


Figure 1 | **PDE5 inhibitors.** Sildenafil (**1**), zaprinast (**2**), vardenafil (**3**) and tadalafil (**4**) are phosphodiesterase 5 (PDE5) inhibitors that are now on the market or are in clinical trials.

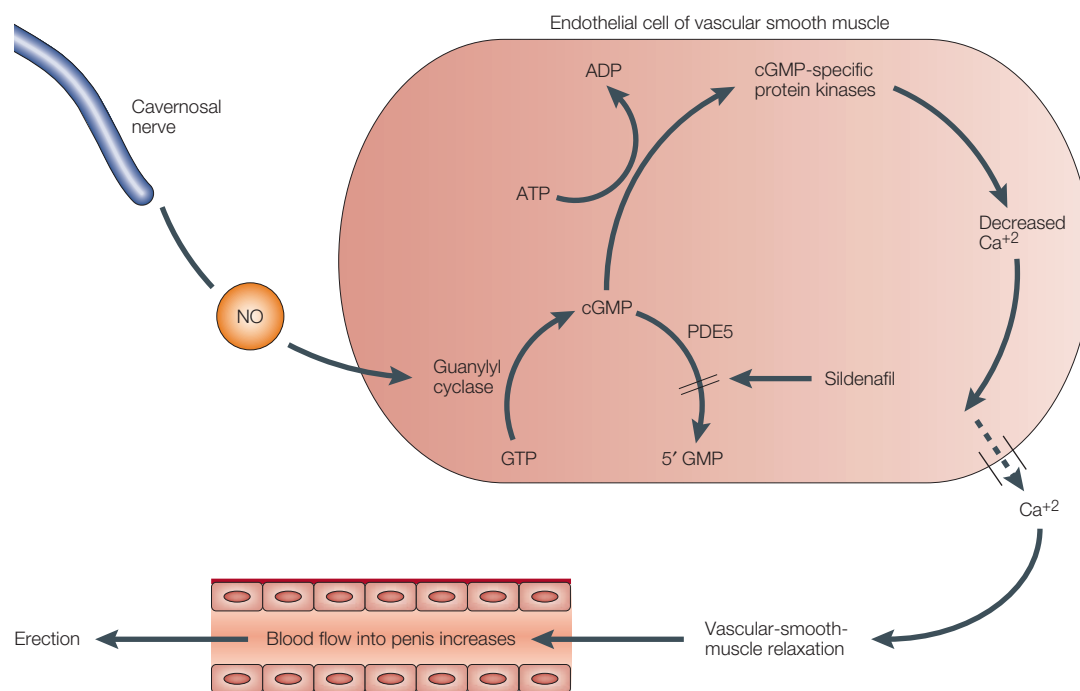


Figure 2 | **Cellular mechanism of action of PDE5 inhibitors.** Erection is initiated by sexual stimulation, which causes the release of nitric oxide (NO) from nerves and cells in the penis. NO diffuses into cells, where it activates the enzyme guanylyl cyclase, which synthesizes cyclic GMP, an intracellular second-messenger molecule. Phosphodiesterase 5 (PDE5) is an intracellular enzyme that degrades cGMP. Inhibition of this activity permits the cyclic nucleotide to remain active as a second messenger, leading to the physiological outcome (erection) illustrated in the graphic below the diagram.

ED comprises men over the age of 40. Many men in this age group also have other chronic diseases, such as depression, diabetes, atherosclerosis, hypertension or ischaemic heart disease. All of these conditions increase the risk of developing ED, and in some cases, the pharmacological treatment for the disorder can also induce ED. Consequently, the safety and efficacy of sildenafil and other PDE5 inhibitors in this group of patients needed to be established.

Several studies have been done with sildenafil in men with cardiovascular disease. The data indicate that, with the exception of patients taking organic nitrates, sildenafil does not have a synergistic effect on blood pressure with antihypertensive agents, such as ACE inhibitors, α -adrenoceptor or β -adrenoceptor blockers, calcium-channel blockers or diuretics¹³. There was no increase in the incidence of drug-related adverse events, and the overall safety profile indicated that there was no significant difference in the incidence of stroke, myocardial infarction or other serious cardiovascular events in patients taking sildenafil. The drug improved erectile function in up to 70% of men with ischaemic heart disease¹⁴, and gave similar results in trials with other groups of men with cardiovascular disease¹³.

In a small study of men with diabetes¹⁵, a 50-mg dose of sildenafil improved erectile function in 52% of patients, as judged by RigiScan (penile PLETHYSMOGRAPHY; developed by **Timm Medical Technologies**) measurements after visual stimulation, diary results of successful sexual intercourse and interviews with patients and partners. The placebo response in this study was 10%.

PLETHYSMOGRAPHY
The measurement and recording of changes in volume of an organ or structure.

As noted in trials in men with pre-existing cardiovascular disease, adverse events were mild and the drug was well tolerated.

Spinal-cord injury can also cause ED, and depending on the site and severity of the injury, sildenafil can be used to improve sexual function. The results of a 28-day study of sildenafil in men with a spinal-cord injury at T6 (thoracic vertebrae 6) through L5 (lumbar vertebrae 5) indicate that a 50-mg dose taken one hour before sexual activity resulted in substantially improved erectile function in 75% of patients who received the drug, compared with just 7% of those patients who were treated with placebo¹⁶. In patients taking sildenafil, a significant improvement in satisfaction with their sex life was reported. An open trial of sildenafil in men with antidepressant-induced sexual dysfunction indicated that a 50–100-mg dose taken as needed over at least four weeks led to statistically significant improvements in libido, arousal, orgasm, sexual satisfaction and erectile function¹⁷. Patients in the study were being treated for depression with either a selective serotonin-reuptake inhibitor or **mirtazapine**.

The New Drug Application (NDA) for vardenafil was submitted to the FDA for approval in September 2001. If approved, the drug will be co-marketed by **Bayer** and **GlaxoSmithKline**. The results from clinical studies with the compound have begun to be reported. It seems that the improved *in vitro* PDE5 IC₅₀ value for vardenafil of 0.7 nM (REF. 18), compared with a value of 3.0 nM for sildenafil¹⁹, contributes to improved potency in man. The typical dose range for vardenafil is 5–40 mg, whereas for

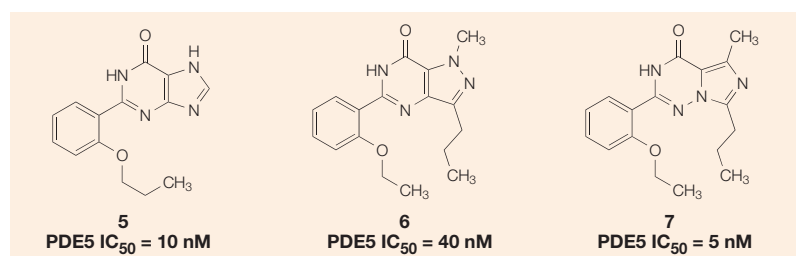


Figure 3 | PDE5 inhibition by pyrimidine isosteres. These compounds show that phosphodiesterase 5 (PDE5) will accept different ring systems as substitutes for cyclic GMP. These inhibitors have different potency as PDE5 inhibitors. The data show that the core ring system found in vardenafil (imidazotriazene ring; compound **7**) is intrinsically more potent than that found in sildenafil (pyrazolopyrimidine ring; compound **6**). Compound **5**, 2-phenyl-substituted purine.

sildenafil, the typical range is 25–100 mg. Initial pharmacokinetic results showed that after single 10-mg or 20-mg doses of vardenafil, C_{\max} (maximum concentration) values of 9.1 and 20.9 $\mu\text{g l}^{-1}$, respectively, were achieved with T_{\max} (time to reach maximum concentration) values of 0.7 and 0.9 hours, respectively. The half-life of vardenafil (four hours) is comparable to that of sildenafil²⁰. These doses also resulted in dose-related increases in penile rigidity and tumescence after visual stimulation. All patients in this study had mild to moderate ED, and all erectile function data were compared with placebo.

A Phase IIb trial of 601 patients with mild to moderate ED used 5-, 10- and 20-mg doses over 12 weeks to measure efficacy in a double-blind, placebo-controlled format²¹. Vaginal penetration and maintenance of erection were the primary end points. Statistically significant improvements were recorded at all three doses for both end points. Successful intercourse was achieved between 71% and 75% of the time in the drug-treated groups. The primary adverse events were headache, flushing, dyspepsia and rhinitis. The frequency of these events was dose related, and was similar to those reported for sildenafil. No cases of visual disturbances were reported.

Another Phase II trial showed that vardenafil was effective in men with severe ED after nerve-sparing radical prostatectomy. After three months using 10- or 20-mg doses, patients recorded successful penetration and maintenance of erection significantly more often than placebo-treated men (47% compared with 22%, and 36% compared with 10%, respectively, for each end point)²². Data from two Phase III studies were pooled to evaluate the safety and efficacy in hypertensive men with mild to moderate ED. The drug was dosed at 5, 10 or 20 mg, and all three groups reported results far superior to placebo. Side effects were generally mild, as noted above, and did not occur more frequently in the hypertensive patient population²². A smaller study showed that a single 10-mg dose of vardenafil did not increase the risk of exercise-induced cardiac ischaemia in patients with stable coronary artery disease²².

Tadalafil received an approvable letter in the United States in April 2002, with final clearance for marketing

pending further clinical-pharmacology studies²³. It has been speculated that these studies will focus on providing extra safety evidence in view of the potential for recreational use of the drug, and because tadalafil has a much longer half-life than sildenafil (17 hours²⁴), leading to a prolonged period of efficacy of up to 36 hours²⁵. Tadalafil also has a more rapid onset of action than sildenafil, often showing effects in 20 minutes or less²⁶. It is likely to be contraindicated in patients taking organic nitrates, in spite of a substantial increase in PDE5 selectivity compared with other phosphodiesterase enzymes²⁴. In healthy subjects who received a single 20-mg dose, there was no significant change in heart rate, standing systolic or diastolic blood pressure²⁴.

Analysis of the data from Phase III clinical trials showed that the incidence of adverse events in patients taking tadalafil, including those with various cardiovascular diseases, was no different from that in placebo-treated patients²⁷. In double-blind, placebo-controlled Phase III trials that included over 1,100 men, tadalafil doses of 2.5–20 mg once daily, as needed, significantly improved erections in up to 81% of men. The mean percentage of successful intercourse attempts was 75%, and efficacy was maintained in both hypertensive and non-hypertensive patient groups²⁸.

There are other PDE5 inhibitors in earlier stages of clinical development, and — on the basis of an evaluation of patent publications — it seems that several companies have preclinical discovery programmes. **Pfizer** has reported that a 'second generation' PDE5 inhibitor, UK369003, is now in Phase II trials for ED. **Vivus** is investigating TA-1790 in Phase I trials. TA-1790 is reported to be a potent, fast-acting and highly selective PDE5 inhibitor, which was licensed from **Tanabe Pharmaceutical**²⁹. **Dong-A Pharmaceutical** entered DA-8159 into clinical trials for ED in April 2002 (REF. 30). DA-8159 is a pyrazolopyrimidinone that has shown erectogenic activity after oral administration of 0.3–1.0 mg kg⁻¹ to rats. In anaesthetized dogs, intravenous administration of 1–300 $\mu\text{g kg}^{-1}$ potentiated an increase in intracavernosal pressure in a dose-related manner³¹. **Eisai** began investigating E8010/4010 in Europe in early 2001 for ED (information obtained from the **Investigational Drugs Database**).

Preclinical studies of PDE5 inhibitors

The design of the imidazotriazene ring system of vardenafil was based in part on the hypothesis that this ring system would prevent metabolism by the enzyme **xanthine oxidase**¹⁸. The imidazotriazene heterocyclic core of vardenafil is a known purine isostere, and comparison of the PDE5 inhibitory activity of 2-phenyl-substituted purine (compound **5** in FIG. 3), pyrazolopyrimidine (compound **6**) and imidazotriazene (compound **7**) indicated that the latter could provide novel, potent PDE5 inhibitors¹⁸. Substitution of the pendant phenyl ring with a piperazine sulphonamide improved potency further, leading to the development of vardenafil, which is more potent and selective than sildenafil for PDE5 *in vitro*.

TUMESCENCE
Becoming swollen.

ISOSTERE
Isosteres are atoms or functional groups of similar size and molecular orientation relative to each other.

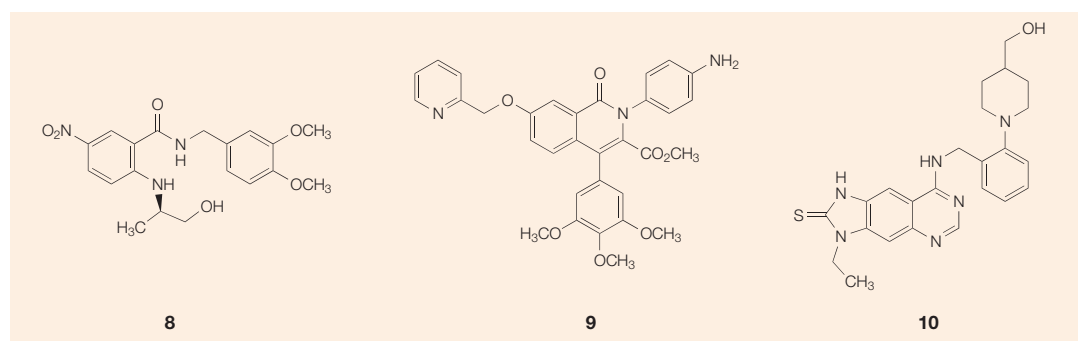


Figure 4 | **PDE5 inhibitors that are structurally unrelated to sildenafil.** The inhibitors FR226807 (**8**), T-1032 (**9**) and KF31327 (**10**) are examples of compounds that are structurally unrelated to sildenafil, but are potent phosphodiesterase 5 (PDE5) inhibitors.

FR226807 (compound **8** in FIG. 4), is a nitrobenzamide derivative that was discovered by **Fujisawa Pharmaceuticals**³¹. The compound is a weak (IC_{50} = 5 μ M) inhibitor of PDE1–4, and has an IC_{50} of 20 nM for PDE6 and an IC_{50} of 1.1 nM for PDE5. *In vitro*, FR226807 relaxes rabbit corpus-cavernosum tissue in a dose-dependent manner. When tested in anaesthetized dogs, 0.1 mg kg⁻¹ given intravenously increased intracavernosal pressure in response to electrical stimulation of the pelvic nerve. Doses of 0.01, 0.032 and 0.1 mg kg⁻¹ FR226807 decreased mean arterial pressure in anaesthetized dogs to approximately the same extent (~8% decrease), unlike sildenafil, which, over the same dose range, gave a dose-related decrease in mean arterial pressure. It was suggested that the significantly improved specificity of FR226807 for PDE5 over PDE1 contributed to this observation. Clinical evaluation of this compound would have to be undertaken with care, as it contains a nitro-aromatic fragment that can be metabolically transformed to generate potentially toxic species, such as nitroso and hydroxylamine derivatives.

The isoquinolone derivative T-1032 (compound **9**) is being studied by Tanabe Pharmaceutical (FIG. 4). T-1032 is a potent (IC_{50} = 1.0 nM) and selective PDE5 inhibitor, with IC_{50} values of greater than 3 μ M against PDE1–4 and 28 nM for PDE6 (REF. 32). T-1032 increased the concentration of cGMP in a dose-dependent manner in rat vascular-smooth-muscle cells over a concentration range of 1–100 nM. There was no change in the level of cAMP in these cells over the same concentration range. When studied *in vitro* using rat aorta and rabbit corpus-cavernosum tissue, T-1032 caused an endothelin-dependent relaxation of aortic tissue along with an increase in cGMP, and potentiated the relaxation induced by the NO donor sodium nitroprusside³³. In rabbit corpus-cavernosum strips, T-1032 was equipotent with sildenafil, as measured by the enhancement of relaxation of the tissue. This might be due to differences in the propensity of T-1032 to efficiently partition into cells in which the target PDE5 is located. The compound was further tested *in vivo* using anaesthetized rats to evaluate effects on venous compliance³⁴. When infused over a dose range of 0.1–10 μ g kg⁻¹ min⁻¹, T-1032 decreased mean arterial pressure (3.8–16.8% relative to control measurements) and mean circulatory filling

pressure (6.1–18.6% relative to control measurements) in a dose-dependent manner. T-1032 at 3 μ g kg⁻¹ increased venous compliance relative to untreated control animals.

The detailed structure–activity relationships that led to the development of T-1032 were reported by Ukita *et al.*³⁵. Three key positions were investigated: substituents on the lactam nitrogen, the 4-aryl ring and the ether moiety. Various 3- and 4-substituted aromatic derivatives, along with saturated carbo- and heterocyclic, as well as alkyl substituents on the lactam were prepared. Of these, the 4-aminobenzene analogue was found to be optimal. On the 4-aryl ring, a 3,4,5-trimethoxy substitution was preferred over either a 4-bromo- or 4-methyl-3,5-dimethoxy arrangement. Finally, the 2-pyridylmethyl ether was equivalent to the 3- and superior to the 4-pyridylmethyl isomer.

Unlike other known PDE5 inhibitors, the imidazoquinazoline KF31327 (compound **10**; FIG. 4) binds in a non-competitive manner with cGMP³⁶. Using PDE1–5 isolated from canine trachea, KF31327 gave IC_{50} values of 380, 670, 38, 800 and 0.074 nM, respectively. In the presence of nitroglycerin, KF31327, over a dose range of 1–100 nM, inhibited platelet aggregation of washed rabbit platelets in a dose-dependent manner, up to a maximum of 60% inhibition of platelet aggregation. Sildenafil showed similar activity in this assay. Interestingly, in the absence of nitroglycerin, KF31327 could also inhibit aggregation at concentrations of between 1–10 μ M, whereas sildenafil at the same concentration had no effect. Cyclic-nucleotide levels were measured in platelet samples after treatment, and in nitroglycerin-treated cells, only cGMP levels increased. However, in the absence of nitroglycerin, treatment with KF31327 resulted in elevated levels of both cAMP and cGMP. The increased levels of cAMP probably occur as a result of inhibition of PDE3 by KF31327. Other known PDE3 inhibitors, such as **milrinone**, can also inhibit platelet aggregation and elevate cAMP levels in platelets.

A group from **SK Chemicals** (South Korea) has reported the structure–activity relationships of sildenafil analogues in a series of papers. The first group of compounds included fused oxygen heterocycles³⁷; for example, compound **11** in FIG. 5. By examining ring size, number of HETEROATOMS and the resulting effect on

HETEROATOMS
Atoms other than carbon or
hydrogen in a molecule.

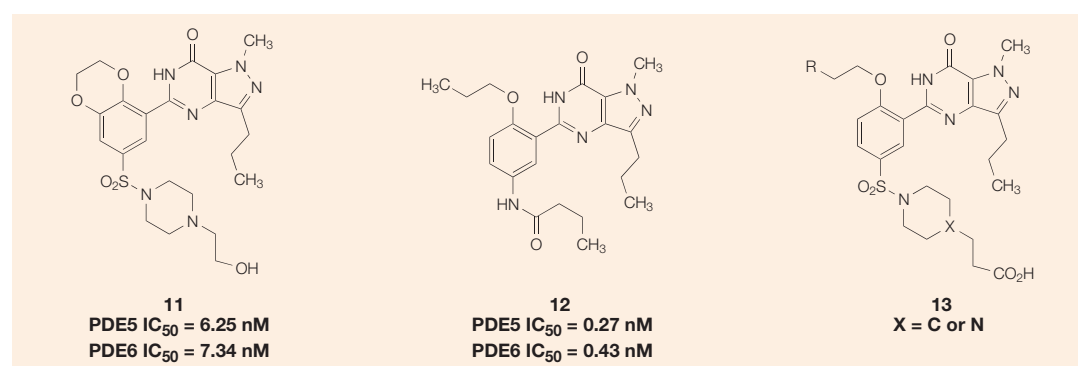


Figure 5 | **PDE5 inhibitors based on the structure of sildenafil.** The phosphodiesterase 5 (PDE5) inhibitors compounds **12** and **13** (SK Chemicals) illustrate variations to the sildenafil structure that lead to improved potency. Neither of these compounds is more selective than sildenafil for PDE6. Compound **11** investigated structure–activity at the alkoxy-ether position.

the TORSION angle between the pyrazolopyrimidine and the pendant bicyclic ring, the researchers attempted to establish a correlation between PDE5 potency and the torsion angle. The latter property was estimated on the basis of *ab initio* calculations. The most potent analogue (compound **11**) had a six-membered ring fused to the aromatic piperazinyl sulphonamide ring, and the torsion angle most closely approximated that of sildenafil. None of these compounds showed an increase in selectivity for PDE5 over PDE6. In fact, this series is less selective than sildenafil for PDE5 over PDE6, and all compounds were less potent against PDE5.

The second paper from this group investigated sildenafil analogues in which the piperazine sulphonamide was replaced by a small set of anilinoamides³⁸ (FIG. 5). This limited study resulted in compounds that were more potent than sildenafil, but once again were less selective for PDE5 over PDE6. In the group of five

new compounds, the most potent was the *n*-butyryl amide (compound **12**). It is possible that some of the increase in potency is due to extension of the alkyl ether from an ethyl to an *n*-propyl chain, an observation made earlier by others³⁹.

To follow up on the strategy of exploring structure–activity at the piperazine sulphonamide locus, this same group also reported on a series of piperazine and piperidine sulphonamides containing a carboxylic-acid moiety that might serve as a mimic of the phosphate moiety of cGMP⁴⁰. This was investigated in parallel with a comparison between ethoxy and propoxy ethers (FIG. 5). When piperidine and piperazine sulphonamides were compared, the former were more potent and the optimal chain length for the carboxylic-acid moiety was found to be three carbons. As noted above, all of the analogues reported in this paper proved to be more potent than sildenafil against PDE5, and all compounds had lower selectivity for PDE5 over PDE6. Selectivity comparisons with PDE1 and PDE3 were reported for selected compounds, and these proved to have similar specificity to sildenafil.

A novel series of pyrazolopyridines was identified by Bi and co-workers⁴¹ on the basis of earlier work at Bristol-Myers Squibb³⁹. Substituents at R_1 and R_2 (FIG. 6) were varied, and it was observed that when these substituents were hydrogen, PDE5 potency and selectivity were comparable to sildenafil. These properties were maximized by adding a 4-fluorobenzylamino moiety at R_1 to give compound **15**, resulting in a PDE5 inhibitor with an IC_{50} of 0.31 nM, which does not inhibit PDE1–4 up to 10 μ M, and is 160-fold selective for PDE5 over PDE6.

A more simple series of pyrazolopyridines was described by Yu *et al.*⁴² (FIG. 6). This series was identified by directed screening of compounds based on a pyrazoloquinoline (compound **16**), reported by Sanofi-Winthrop⁴³. The ester lead (compound **17**) was optimized at both the 4-amino and carboxy sites by parallel synthesis. This generated the 4-(3-chloro-4-methoxybenzylamino)-4-pyridylmethyl amide (compound **18**), which has a PDE5 IC_{50} of 0.8 nM, and is approximately 50-fold selective for PDE5 over PDE6. Compound **18** has good oral bioavailability (66%) in dogs with a two-hour

TORSIONAL
The freedom or ability to rotate
along a defined angle.

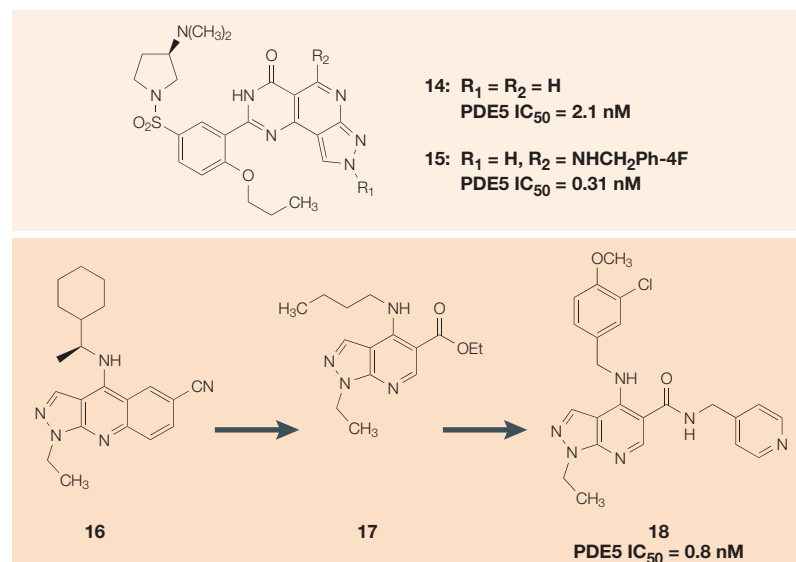


Figure 6 | **Novel pyrazolopyridine PDE5 inhibitors.** The phosphodiesterase 5 (PDE5) inhibitors compounds **14** and **15** (Bristol-Myers Squibb) are related to PDE5 inhibitors that were previously disclosed by Bristol-Myers Squibb. Compound **18** was designed on the basis of compound **16**, which was disclosed by Sanofi–Winthrop.

half-life and efficacy equal to that of sildenafil in an *in vitro* rabbit corpus-cavernosum tissue-strip assay³⁹. In spite of these promising properties, the compound inhibited certain cytochrome P450 enzymes (CYP enzymes) and blocked the **HERG** potassium channel, so it was not advanced for further testing.

Recently, Yu has described yet another series of PDE5 inhibitors that have been evaluated in Phase I trials in healthy men (G. Yu *et al.*, unpublished observations) (FIG. 7). These pyrazolopyridopyridazines were designed on the basis of the observation of an intramolecular hydrogen bond between the amide carbonyl and 4-amino NH moiety in compound 18, which stabilizes a particular conformation of the molecule and forms a pseudo 'ring-like' structure. In this series, the ethyl group on the pyrazole ring and the 3-chloro-4-methoxybenzylamino moieties are optimal, with substituted imidazoles (compound 19) at R₁ on the pyridazine ring giving potent (PDE5 IC₅₀ < 1 nM), selective (IC₅₀ > 10⁴ for PDE1–4, 150-fold more selective for PDE5 than PDE6) compounds. An *N*-methylamide analogue (compound 20) showed good oral bioavailability in dogs (42%), with a two-hour half-life. In humans, a dose-related increase in drug levels in plasma was measured over a dose range of 2–50 mg. There were no visual disturbances noted at the 50-mg dose. However, some patients did report headaches after doses of 25 and 50 mg. In humans, the compound is mainly metabolized by **CYP2D6**, and has a half-life greater than 12 hours.

So far, PDE5 inhibitors have shown efficacy for the treatment of ED only in men. However, the same principles are potentially applicable in the treatment of certain types of sexual dysfunction in women, namely by increasing blood flow to the genitals. The ability of sildenafil to relax rabbit clitoral corpus-cavernosum tissue was shown *in vitro*⁴⁴. Pre-treatment of tissue strips with 100-nM sildenafil was shown to enhance relaxation of this smooth muscle after electrical-field stimulation. In anaesthetized rabbits, sildenafil was administered by intravenous infusion over a dose range of 0.21–2.1 µg kg⁻¹ to achieve blood levels of between 5 and 50 nM. At the highest dose, it was shown that sildenafil increased blood flow in the clitoris, decreased vaginal luminal pressure and increased vaginal lubrication after pelvic-nerve stimulation⁴⁵. Clinical trials of sildenafil in postmenopausal women have failed to show efficacy, for reasons that are poorly understood, and might depend on the nature of sexual dysfunction⁴⁶. However, Caruso and co-workers have shown that in a small group of premenopausal women, both arousal and orgasm were improved relative to placebo-treated patients⁴⁷.

Other actions of PDE5 inhibitors

The potential use of PDE5 inhibitors for the treatment of **cystic fibrosis** was shown by McPherson and co-workers⁴⁸, who used IBMX (3-isobutyl-1-methylxanthine) *in vitro* to stimulate mucin secretion in submandibular cells as a model for this severe pulmonary disorder. IBMX was tested at high concentrations (1 mM), and was shown to elevate levels of cGMP in

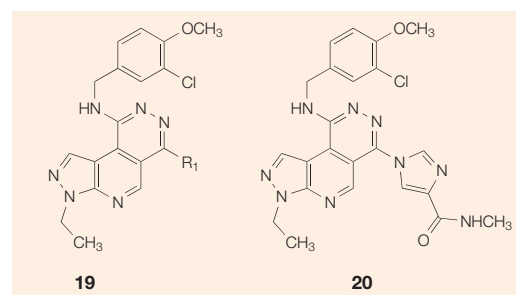


Figure 7 | **PDE5 inhibitors based on pyrazolopyridopyridazine**. These phosphodiesterase 5 (PDE5) inhibitors have a pyrazolopyridopyridazine structure. Compound 20 has been investigated in Phase I trials in humans.

these test cells. However, at this concentration, other PDEs are also likely to be inhibited. The effects of sildenafil on gastrointestinal function in humans has been investigated. Bortolotti has shown that a 50-mg dose of sildenafil reduced lower-oesophageal-sphincter tone and residual pressure compared with placebo in patients with idiopathic achalasia⁴⁹. Achalasia is a disorder characterized by a reduced ability to move food down the oesophagus, and an inability of the lower oesophageal sphincter to relax in response to swallowing. In normal control subjects, the same 50-mg dose of sildenafil inhibits interdigestive motor activity of the antrum and duodenum as it decreases the number and amplitude of contractions by this smooth-muscle tissue⁵⁰. This property could be associated with the dyspepsia that has been noted in patients taking PDE5 inhibitors. The authors note that the effect is rapidly reversible in patients with normal gastrointestinal function, but speculate that caution should be exercised if the drug is to be used in patients with established, delayed gastric emptying or gastroparesis.

PDE5 inhibitors exert their action in ED by dilating arteries and increasing blood flow to the penis. This vasodilatory property has also been investigated in the context of other circulatory disorders. In a recent report⁵¹, improved haemodynamic function in patients with established pulmonary hypertension who were treated with the prostaglandin analogue iloprost was recorded, and the duration of the effect was extended by the addition of up to 50-mg sildenafil. The five patients in this study, when given both sildenafil and iloprost, showed an enhanced reduction in pulmonary arterial pressure (–13.8 mm Hg), compared with iloprost (–9.4 mm Hg) or sildenafil (–6.4 mm Hg) alone. This effect persisted for up to two hours after the PDE5 inhibitor was administered, whereas when patients were given iloprost alone, pulmonary arterial pressure returned to pre-treatment levels after two hours. There was no significant change in heart rate or systemic arterial pressure during the treatment.

Subarachnoid haemorrhage is a significant cause of stroke in many patients. It often arises as a consequence of reduced responsiveness to NO in cerebral arteries. To counter this effect pharmacologically, it has been proposed⁵² that PDE5 inhibitors will elevate cellular levels of cGMP in cerebral arteries to counteract this vascular

dysfunction. Experimentally, the usefulness of sildenafil has been shown in a rat model of cerebral ischaemia⁵³. Oral administration of either 2 or 5 mg of sildenafil two hours after induction of ischaemia, and continuing for six days, significantly improved test scores for neurological deficits in test animals. Furthermore, a reduction in infarct volume was measured in animals treated with 2-mg sildenafil compared with untreated controls.

As noted above for KF31327, sildenafil can also modulate platelet aggregation in a dose-dependent manner⁵⁴. Administration of either 50 or 100 mg sildenafil as a single dose to healthy volunteers was followed by *ex vivo* platelet-aggregation assays in platelet-rich plasma at zero, one and four hours after the dose. The lower dose had no effect on platelet aggregation at any of the time points studied in response to either collagen or ADP-induced stimulus. However, the 100-mg dose did prolong aggregation time at one hour in response to collagen. At the four-hour time point, platelet aggregation returned to normal. Sildenafil did not inhibit ADP-induced aggregation at either dose.

Conclusions

PDE5 inhibitors have shown usefulness in the treatment of ED in men, and by 2003, it is possible that three compounds will be approved for use in the United States: sildenafil, vardenafil and tadalafil. There is continuing interest in the discovery and optimization of new PDE5 inhibitors, as reflected by the number of recent publications in the patent and peer-reviewed literature. Some of the compounds described in such reports are both more potent and more selective than sildenafil. The application of PDE5 inhibitors to treat female sexual disorders is being investigated clinically, and both preclinical and clinical studies have shown that such compounds might also be useful in other disorders in which smooth-muscle dilation is involved. If any of these efforts are successful, PDE5 inhibitors will no longer be considered only as 'quality-of-life' drugs. This is a substantial and promising field of research that continues to grow, and will be of interest to both biological and chemical scientists for the foreseeable future.

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Online summary

- Phosphodiesterase 5 (PDE5) inhibitors are useful for the treatment of erectile dysfunction (ED), and a wide variety of chemotypes have shown activity as PDE5 inhibitors.
- PDE5 inhibitors work in conjunction with sexual stimulation to induce erection, and have a low risk of priapism.
- Clinical studies with sildenafil, vardenafil and tadalafil indicate that these compounds are efficacious for the treatment of ED that is a consequence of various causes, and are safe for use in most patients.
- Vardenafil and tadalafil have been submitted for regulatory approval in the US and European markets. Final approval and marketing of these compounds is pending the outcome of regulatory review.
- There is substantial activity in the discovery of novel PDE5 inhibitors, some of which are more potent and selective than sildenafil *in vitro*.
- PDE5 inhibitors have also been investigated for actions on other tissues, including the gastrointestinal tract and the circulatory system. PDE5 inhibitors have been shown to reduce blood pressure in patients with pulmonary hypertension, and in animal models, have potential for use in the treatment of stroke.

About the author

David P. Rotella is a principal scientist at Bristol-Myers Squibb (BMS) in Hopewell, New Jersey. At BMS, in addition to his work on the discovery and development of phosphodiesterase 5 (PDE5) inhibitors, he has been involved in projects to discover novel chemokine (C-C motif) receptor 2 (CCR2) and calcium-sensing receptor antagonists, as well as dipeptidylpeptidase 4 (DPP4) inhibitors for the treatment of type II diabetes. While at Cephalon, he initiated the discovery of novel K252A analogues, some of which are now being clinically investigated for central nervous system and cancer applications. He is the author of 22 papers and is a co-inventor on five patents.